

**REMARKS**

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

**I. CLAIM STATUS & AMENDMENTS**

Claims 1-5 are pending in this application, and stand rejected.

The specification has been amended to reflect that the application is 371 National Stage application.

Claims 1 and 3-5 have been amended.

Claim 1 has been amended to clarify that the human gene over-expressing animal expresses human prostaglandin D2 synthase in the lung, spleen and liver at a level more than five times that of a wild-type animal as supported by the disclosure, for instance, in Figure 4.

Claims 1 and 3-5 have been amended to provide antecedent basis for the “animal” obtained by ontogenesis.

Claims 1 and 3-5 have been amended to clarify that the “animal” obtained by ontogenesis is the “human gene over-expressing animal.” Support for this amendment can be found in the claims as originally filed.

Claims 3-5 have also been amended to clarify the candidate substance being administered in the claimed method. Support for this amendment can be found in the claims as originally filed.

Therefore, no new matter has been added by this amendment.

**II. FOREIGN PRIORITY**

Kindly acknowledge Applicants’ claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f), as well as receipt of the certified copies of the foreign priority document.

### III. ANTICIPATION REJECTION

Claims 1-5 were rejected under 35 U.S.C. § 102(b) as anticipated by Urade, Nippon Rinsho Feb, Vol. 56, No. 2, pp. 488-92 (1998). See page 2 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims.

To anticipate a claim, a cited prior art reference must teach each and every element of the claimed invention. M.P.E.P. § 2131.01.

The claims call for a human gene over-expressing animal, which is a non-human animal carrying a human hematopoietic prostaglandin D2 synthase gene in its somatic cell chromosome and expressing human prostaglandin D2 synthase in the lung, spleen and liver at a level more than five times that of a wild-type animal.

Urade fails to disclose or suggest these limitations.

On page 2 of the Office Action, it is indicated that Urade discloses “human PGD2 synthase transgenic mice” and “human hematopoietic PGD2 synthase” of the present invention and that “human PGD2 synthase” in Urade is a different name for the same synthase in the present invention. However, it is respectfully submitted that this characterization of Urade is incorrect.

The human hematopoietic PGD2 synthase and human PGD2 synthase are different synthases. In this regard, the human PGD2 synthase in Urade is a “lipocalin-type PGD2 synthase” which is mainly over-expressed in the brain (see GenBank/NM000954). In contrast, in the present invention, the hematopoietic PGD2 synthase (see GenBank/NM014485) is over-expressed in hematopoietic organs, such as the spleen and liver. Please note that the art recognizes and distinguishes these differences (PGD2 synthase (brain) and PGD2 synthase (hematopoietic)) as evidenced by GenBank/NM000954 and GenBank/NM014485.

Therefore, the transgenic mice of Urade which over-express lipocalin-type PGD2 synthase in the brain are clearly and unobviously different from the transgenic animal of the present invention which over-expresses hematopoietic PGD2 synthase in hematopoietic organs.

Accordingly, Urade fails to disclose or suggest a non-human transgenic animal carrying a human hematopoietic prostaglandin D2 synthase gene and which expresses human prostaglandin D2 synthase in the lung, spleen and liver at a level more than five times that of a wild-type animal. As such, Urade fails to disclose or suggest each and every element of the claimed invention.

In view of the above, the rejection of claims 1-5 under 35 U.S.C. §102(b) is untenable and should be withdrawn.

#### **IV. OBVIOUSNESS REJECTIONS**

Claim 3 was rejected under 35 U.S.C. § 103(a) as obvious over Urade and Shichijo et al., Clinical and Experimental Allergy, Vol. 28, pp. 1228-1236 (1998). See pages 2-4 of the Office Action.

Claim 4 was rejected under 35 U.S.C. § 103(a) as obvious over Urade and Hayaishi, The Journal of Biological Chemistry, Vol. 263, No. 29, pp. 14593-14596 (1988). See pages 4-5 of the Office Action.

Claim 5 was rejected under 35 U.S.C. § 103(a) as obvious over Urade and Haberl et al., Mediators of Inflammation, Vol. 7, pp. 79-84 (1998) and Reginato et al., The Journal of Biological Chemistry, Vol. 273, No. 4, pp. 1855-1858 (1998). See pages 5-6 of the Office Action.

These rejections are respectfully traversed as applied to the amended claims for the same reasons noted above with regard to Urade and for the following reasons.

To establish obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. M.P.E.P. § 2143.03. Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. M.P.E.P. § 2143.01. Third, the prior art must provide a reasonable expectation of success. M.P.E.P. § 2143.02.

As discussed above, Urade fails to disclose or suggest each and every element of the claimed invention, namely, a non-human transgenic animal carrying a human hematopoietic prostaglandin D2 synthase gene, which expresses human prostaglandin D2 synthase in the lung, spleen and liver at a level more than five times that of a wild-type animal.

Again, the transgenic mice of Urade mainly over-express the PGD2 synthase in brain, and thus, are usable for testing the effects of PGD2 in brain. In contrast, the transgenic animal of the present invention over-express the synthase in hematopoietic organs, and as such, the mass-production of PGD2 in the these organs can be tested.

The secondary references of Shichijo, Hayaishi, Haberl and Reginato fail to remedy the deficiencies in Urade. Even though these references disclose the topical effects of PGD2, they fail to suggest the methods of claims 3-5 which are based on the mechanisms of PGD2 in hematopoietic organs.

In view of the above, the prior art rejections of claims 3-5 under 35 U.S.C. §103(a) are untenable and should be withdrawn.

## **V. ENABLEMENT REJECTION**

Claims 1-5 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the claimed invention. See pages 6-9 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims.

The test of enablement is whether one reasonably skilled in the art could make or use the invention based on the disclosure in the specification coupled with the knowledge in the art without undue experimentation.

On pages 7-8 of the Office Action, it is indicated that only a mouse could be genetically modified at the time of filing of this application. It is respectfully submitted that this characterization of the state of the art is incorrect. At the time of filing, there were many reports

for making transgenic animals, other than mice. For instance, the following references were found from a PubMed web site “transgenic animal” keyword search:

1. Hammer et al., “Production of transgenic rabbits; sheep and pigs by micro-injection, Nature, 315(6021):680-683 (1985);
2. Knight et al., “Transgenic rabbits with lymphocytic leukemia induced by the c-myc oncogene fused with the immunoglobulin heavy chain enhancer,” PNAS USA, 85:3130-3134 (1988);
3. Vise et al., “Introduction of a porcine growth hormone fusion gene into transgenic pigs promotes growth,” J. Cell. Sci., 90 (Pt 2):295-300 (1988); and
4. Mullins et al., “Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene,” Nature, 344(6266):541-544 (1990).

Accordingly, the Office Action’s characterization of the state of the art with regard to transgenic technology is inaccurate. In the Office Action, it is indicated that only mouse ES-cells were known at the time of filing. However, ES-cells are necessary for “gene targeting technology” or “gene knockout technology.” As to transgenic technology, fertilized eggs or early embryos can be used (see page 6, line 10 of the specification).

Thus, at the time of the filing, transgenic animals other than mice had been produced. As such, the skilled artisan upon reading the disclosure and given the knowledge in the art, could make and use the full breadth of the claims without undue experimentation.

In view of the above, the rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

## **VI. INDEFINITENESS REJECTION**

Claims 1 and 3-5 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the reasons set forth on page 9 of the Office Action.

It is respectfully submitted that the present amendment overcomes this rejection for the following reasons.

The claims have been amended to delete the term “expressing a large amount of human prostaglandin D2 synthase” in claim 1.

Also, the phrase “sleep-controlling substance” in claim 4 has been changed to “sleep-lowering substance” as supported by Example 3 of the disclosure. Example 3 on page 10 involves a study of narcolepsy and indicates that the sleep time of the transgenic mice was increased.

Finally, the term “differentiation-controlling” in claim 5 has been replaced with “body weight-lowering substance” as supported by Example 4. Example 4 demonstrates that the body weight of the transgenic mice was significantly increased over that of the wild-type mice.

For these reasons, the rejection of claims 1 and 3-5 under 35 U.S.C. § 112, second paragraph, is untenable and should be withdrawn.

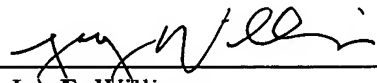
**CONCLUSION**

In view of the foregoing amendments and remarks, the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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